Several amendments have been made to the specification to correct typographical errors. No new matter has been introduced with these amendments to the specification.

The pending application is a continuation of parent application, U.S. Serial Number 08/366,051, filed December 29, 1994, now U.S. Patent No. 5,650,283, which is a continuation-in-part application of U.S. Serial Number 08/045,806, filed April 8, 1993, now U.S. Patent No. 5,378,822.

In the Office Action, the Examiner rejected claims 1, 2, 4 to 6 and 8 to 20 under the judicially created doctrine of obviousness-type double patenting. Applicants will submit a terminal disclaimer or traverse this rejection upon notification of allowable subject matter.

In the Office Action of the subject application, the Examiner rejected claims 1-2, 4-6, 8-12 and 14-20 under 35 U.S.C. § 112, first paragraph. More specifically, the Examiner states that the disclosure is enabling only for claims limited to an Ah receptor protein having the amino acid sequence presented in either SEQ ID. Nos. 2 or 4 of the specification because these were the only Ah receptors described in the specification. The Examiner relies on Amgen Inc. v. Chugai Pharmaceuticals Co., Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991), in support of this rejection. Moreover, the Examiner makes the following additional points:

1. The claims encompass a cell containing a plasmid which encodes an Ah receptor having other than a natural amino acid sequence. The specification does not identify those amino acid residues in the amino acid sequences of SEQ ID. Nos: 2 and 4 which are essential for the biological activity and structural integrity of those proteins and those residues which are either expendable or substitutable. Without this information, one of ordinary skill in the art would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of over 800 amino acid residues before they could even begin to rationally design a functional Ah receptor protein having other than one of the disclosed natural amino acid sequences. Finally, the disclosure of the two DNAs encoding Ah receptors with natural amino acid sequences is clearly insufficient

under Section 112 for the claims which encompass any and all proteins which may fall within the term "Ah receptor protein".

2. The claim limitations are comparable in scope to those of claim 7 of U.S. Patent Number 4,703,009 which were held to invalid under Section 112, first paragraph, for lack of enablement in Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd. This limitation is in claim 7, according to the Examiner is narrower than the "Ah receptor protein" limitation of the instant claims. The disclosure upon which the claim was based described a recombinant DNA encoding EPO and a few analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes two DNAs, each of which encodes a particular Ah receptor protein, it does not describe even a single variant thereof. The Examiner says that the instant specification is even more limited than the '008 patent because it describes only a single protein and no analogs or mutants thereof and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

The Examiner's rejection of claims 1-2, 4-6, 8-12 and 14-20 under § 112, first paragraph, is without basis in law or fact and the Examiner's reliance on Amgen Inc. v. Chugai Pharmaceutical Co., Ltd. to support this rejection is misplaced. Claim 7 of U.S. Patent 4,703,008, assigned to Amgen, which was one of the claims in litigated in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., reads as follows:

7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

Claim 7 is directed to a purified and isolated DNA sequence. This claim covers all possible DNA sequences that will encode any polypeptide having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of red blood cells. In affirming the trial court's decision that claim 7 was insufficient to enable one of ordinary skill in the art to make and use the invention without undue experimentation, the Federal Circuit held that it is not necessary that a patent applicant tests

all embodiments of his invention, but, that for claims directed to DNA sequences, what is necessary is a disclosure of how to make and use enough sequences to justify grant of claims sought. Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 18 U.S.P.Q.2d 1016, 1027 (Fed. Cir. 1991). The Federal Circuit also stated that:

> ... under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs. Id.

In the present application, the Applicants are not claiming an isolated and purified DNA sequence encoding an Ah receptor or the amino acid sequence of the Ah receptor. Rather, the Applicants are claiming a yeast cell transformed with plasmids expressing certain elements (claims 1-2, 4-6 and 8-10), a mammalian cell transformed with plasmids expressing certain elements (claims 11-12 and 14) and an assay for detecting agonists to the Ah receptor in environmental samples (claims 15-20). For example, claim 1 is directed to a yeast cell transformed with plasmids expressing the Ah receptor protein, the Ah receptor nuclear translocator, the dioxin responsive element and a reporter gene for detecting the activation of Ah receptor in the presence of an Ah receptor agonists. Sequence ID Nos. 2 and 4 are provided in the specification as a particular embodiments illustrative of the various types of Ah receptor protein that could be incorporated into the plasmids. Nonetheless, the claimed invention is the resulting yeast cell having all of these components which together function as a novel cellular mechanism (system) for detecting the presence of entities which bind the Ah receptor. Claim 1 does not attempt to claim the Ah receptor protein as a compound, thereby requiring its limitation to the specific amino acid sequences disclosed in the specification. Additionally, none of the claims in the present application claim the Ah receptor protein as a compound. It appears that instead of focusing on what is

actually being claimed, the Examiner has focused his attention on one specific element of the claims, the Ah receptor protein.

The Examiner states that the specification does not identify those amino acid residues in the amino acid sequences of SEQ ID Nos. 2 and 4 that are essential for the biological activity and structural integrity of those proteins and those residues that are either expendable or substitutable. As discussed above, Applicants are not claiming amino acid sequences for the Ah receptor but instead are claiming yeast and mammalian cells containing plasmids which express certain elements and an assay for detecting agonists to the Ah receptor in environmental samples. Therefore, Sequence ID Nos. 2 and 4 provide particular embodiments illustrative of the various types of Ah receptor protein that could be incorporated into the plasmids that are used to transform the yeast and mammalian cells of this invention.

The Examiner also states that the instant specification only describes a single protein and no analogs or mutants. Again, the claims of the present invention are not directed to a single protein. However, for the Examiner's information, the Ah receptor is defined in terms of its ligand binding domain as well as a series of deletion mutants on pages 16-18 of the specification. Moreover, FIG. 9 sets forth various deletion mutants from both the murine and human versions of the Ah receptor.

The claims of the present application are directed to yeast and mammalian cells that are transformed with plasmids that express certain elements and to an assay for detecting agonists to the Ah receptor in environmental samples. The claims are not directed to DNA or amino acid sequences. The Examiner's reliance on Amgen is misplaced. Applicants claims are enabled by the specification. Therefore, Applicants respectfully

request that the reject of claims 1-2, 4-6, 8-12 and 14-20 under § 112, first paragraph, be removed.

Claims 1,2, 4-6 and 8-20 were also rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Applicants believe that this rejection is rendered moot by the amendments to the claims. Therefore, Applicants respectfully request that this rejection be removed.

Claims 1-2, 4, 15, 16 and 18-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Ema et al. in view of Mak et al. and Hoffman et al. Applicants respectfully traverse this rejection.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, unless there is some teaching or suggestion supporting the combination. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The mere fact that the prior art may be modified in a manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. Id.

In the present application, there is no suggestion or teaching in any of the references cited by the Examiner supporting their combination. Ema et al. disclose the cloning and structure of a complementary DNA encoding a mouse putative Ah receptor. Ema et al. further disclose mammalian cells cotransfected with a plasmid that contains the cDNA of the murine Ah receptor and a plasmid that contains XRE and the CAT gene. Ema et al. state that "[T]hese results indicate that the mode of the Ah receptor function is apparently more complex than that of the steroid receptors and could be different from that of the receptors" (page 251).

Mak et al. disclose the expression of functional chicken oviduct progestrone receptors (steroid hormone receptors) in *Saccharomyces cerevisiae*. The Mak et al. reference also mentions using a reporter plasmid that contains a reporter gene such as the B-galactosidase. The Hoffman et al. reference discloses that the coding sequence of the cDNA of Arnt had been eludicated. Hoffman et al. then inserted this cDNA sequence into mammalian expression vectors. Hoffman et al. also disclose the predicted amino acid sequence of the Arnt protein. However, Hoffman et al. state that the "mode of action of the Ah receptor appears to be more complex than that of the steroid hormone receptors, and particularly the glucocorticoid receptor" (page 958). This statement in Hoffman et al. as well as the similar statement in Ema et al., suggest that the Ah receptor is more complex than steroid hormone receptors. Therefore, Hoffman et al. and Ema et al. provide a motivation against their combination with Mak et al. Additionally, there is noting in any of these references that suggests or motivates their combination. Instead, the Examiner has used "hindsight" to pick and choose references to recreate the present invention.

Assuming *arguendo*, that the above-identified references are combinable, the Examiner has still not met his burden of establishing a *prima facie* case of obviousness. As discussed earlier, Ema et al. disclose the cloning and structure of a complementary DNA encoding mouse putative Ah receptor. Ema et al. also disclose mammalian cells cotransfected with a plasmid that contains the cDNA of the murine Ah receptor and with a plasmid that contains XRE and the CAT gene (which functions as a reporter system). Ema et al. do not disclose transfecting a cell with plasmids that express the Ah receptor, Arnt, a dioxin responsive element and a reporter gene. The Examiner tries to overcome this deficiency by arguing that Ema et al. utilized cells "which presumably expressed Arnt endogenously." However, the Examiner does not provide any support for this assertion. Additionally, Ema et al. do not disclose an assay for detecting dioxin in environmental samples using the cells claimed by the Applicants.

The deficiencies of Ema et al. are not cured with the Examiner's reliance on Mak et al. Mak et al. disclose a yeast cell that contains recombinant DNA encoding the chicken oviduct progesterone receptor. Mak et al. used reporter plasmids to test for progesterone receptor-mediated activation of transcription in yeast. The Examiner states:

[B]ecause the Ah receptor of Ema et al. was functionally analogous to the progesterone receptor of Mak et al. in that each contains a ligand binding domain and a DNA binding domain in which, upon binding ligand, each receptor/ligand complex binds to a DNA response element, an artisan would have found it *prima facie* obvious to have substituted the Ah receptor and XRE of Ema et al. in place of the progesterone receptor and response element of Mak et al. to permit the detection of Ah receptor ligands in a sample by using the genetically simple yeast expression system.

The fact remains that even with the combination of these two references that the claimed invention is still not rendered obvious. Nothing in the combination of these two references discloses or suggests transforming cells with transfecting a cell with plasmids that express the Ah receptor, Arnt, the dioxin responsive element. Also, nothing in these two references discloses or suggests an assay for determining agonists to the Ah receptor in environmental samples.

To cure the deficiencies of the Ema et al. and Mak et al., the Examiner relies on Hoffman et al. Hoffman et al. disclose that the coding sequence of the cDNA of Arnt had been elucidate. Hoffman et al. further disclose the insertion of the coding sequence of the cDNA of Arnt into mammalian expression vectors. Hoffman et. also disclose the predicted amino acid sequence of the Arnt protein. Hoffman et al. do not disclose transforming cells with plasmids that express the Ah receptor, Arnt, a dioxin responsive element and a reporter

gene. In fact, Hoffman et al. disclose that further investigation is required to determine the function Arnt serves in conjunction with the Ah receptor. Hoffman et al. state on page 957:

"Whether Arnt truly directs the Ah receptor to translocate form the cytosol to the nucleus after binding of ligand or whether the unoccupied receptor is, in fact, located in the nucleus and Arnt increases the avidity with which the receptor binds to this organelle requires further investigation."

To support his argument of obviousness based on these three references, the Examiner states that:

"Because the Ema et al. publication shows that the presence of Arnt protein was known to be needed to obtain the transport of Ah receptor/ligand complex to the nucleus of a cell at the time of the instant invention, and artisan would have found it *prima facie* obvious to have included the recombinant DNA encoding the Arnt protein that was described by Hoffman et al. in a yeast cell in conjunction with a DNA encoding the Ah receptor and an XRE reporter plasmid as described by Ema et al. to permit the use of such a cell to detect Ah receptor ligand in a sample in a manner that was directly analogous to that which was described by Mak et al. prior to the time that the instant invention was made."

Applicants disagree with this reasoning. Applicants submit that Ema et al., did not conclusively know whether or not Arnt was needed to obtain the transport of the Ah receptor to the nucleus. On page 250, Ema et al. state:

"...it is interesting to know whether the Arnt protein directly interacts with the putative Ah receptor through the basic helix-loop-helix motif, because the Arnt protein is **proposed** to be involved in the nuclear translocation of the Ah receptor from cytoplasm (Emphasis added)."

Therefore, at the time Ema et al. was published, it was not conclusively known whether or not Arnt was involved in the nuclear translocation of the Ah receptor from the cytoplasm to the nucleus. Again, as discussed earlier, Ema et al. do not disclose or suggest

yeast or mammalian cells transformed with plasmids expressing the Ah receptor protein, Arnt, a dioxin responsive element and a reporter gene, or an assay for determining agonists to the Ah receptor in environmental samples.

None of the references cited by the Examiner disclose or suggest the yeast or mammalian cells claimed by the Applicants. Additionally, none of the references disclose or suggest an assay for detecting agonists to the Ah receptor in environmental samples as claimed by the Applicants. Therefore, the Examiner has not met his burden of establishing a *prima facie* case of obviousness and the Applicants respectfully request that the rejection be removed.

The Examiner has also indicated that the declaration is defective. Applicants wish to forego the filing of a new declaration until the Examiner indicates that some or all of the claims are allowable.

The Draftsperson has also indicated that several corrections need to be made to the drawings. Applicants will file corrected drawings upon indication by the Examiner that some or all of the claims are allowable.

Finally, Applicants herewith submit a Petition for a Three Month Extension of Time and a check for $475.00 to cover the petition fee.

Based upon the above arguments, Applicants respectfully request allowance of the presently claimed invention. Should the Examiner be of the opinion that a telephone conference would aid in the prosecution of the application or that outstanding issues exist, the Examiner is invited to contact the undersigned.

Respectfully submitted,

ROCKEY, MILNAMOW & KATZ, LTD.

By: _____
Lisa V. Mueller, Reg. No. 38,978

Two Prudential Plaza, Suite 4700
180 North Stetson Avenue
Chicago, Illinois 60601
(312) 616-5400

CERTIFICATE OF MAILING

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage at First Class Mail in an envelope addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231 on May 22, 1998.

_____